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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/722,176	11/24/2003	Tariq M. Rana	20336-00016	3047

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CHONG, KIMBERLY	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/722,176	RANA, TARIQ M.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 May 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *14 and 17-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *14 and 17-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/3/07, 1/31/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 05/03/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 01/03/2007 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 05/03/2007, claims 14, 17-44 are pending in the application.

Response to Applicant's Arguments

Re: Claim Rejections - 35 USC § 112

Claims 14 and 17-44 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for the reasons of record filed 01/03/2007.

Applicant points to Figures 6A, 6B and 6C and paragraphs 0025-0027, 0102-0103 and paragraph 0111 for support for "a generation 2 to 5 dendrimer". After further consideration, Figures 6A, B and C do provide support for a generation 2 PAMAM dendrimer, a generation 3 PEG dendrimer and a generation 5 PAMAM dendrimer. The specification however does not provide support for a generation 4 dendrimer.

Applicants submit Examples 1, 2 and 7 utilize a generation 4 dendrimer in the experiments. It is not clear from Examples 1, 2 and 7 which type of dendrimer was used and therefore these Examples do not provide adequate support for the claimed generation 4 dendrimer. Examples 1 and 2 disclose the use of a PAMAM dendrimer in a delivery mixture comprising a siRNA; however the specification does not disclose the use of PAMAM dendrimer is a generation 4 dendrimer. Therefore, because the claims as recited still encompass a generation 4 dendrimer and said dendrimer is not adequately supported in the specification, the claims fail to comply with the written description requirement.

If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity, to where such support is to be found. Therefore, instant claims 14 and 17-44 are accorded a filing date of 11/24/2003.

The rejection of claim 44 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is obviated in response to claim amendments filed 05/03/2007.

Re: Claim Rejections - 35 USC § 102

The rejection of claims 14, 20, 22-24 and 43 under 35 U.S.C. 102(e) as being anticipated by Frecht et al. (U.S. Patent No. 7,097,856) is maintained for the reasons of record in the Office action mailed 01/03/2007.

Applicant's arguments in the response filed 05/03/2007 are acknowledged but not found persuasive. Applicant argues Frecht et al. does not anticipate the instant invention because Frecht et al. teach the dendrimer is conjugated to a desired agent to be delivered whereas the instant invention is drawn to a delivery mixture "i.e. non-conjugated dendrimer-nucleic acid mixture" comprising a dendrimer and a nucleic acid.

Applicant's arguments are not convincing because "a delivery mixture" is not defined in the specification as being limited to a non-conjugated dendrimer-nucleic acid mixture. The claims are broadly drawn to a delivery mixture *comprising* a dendrimer and a nucleic acid, which would encompass a dendrimer conjugated with a nucleic acid molecule. Therefore, Frecht et al. anticipates the instant claims.

Re: Claim Rejections - 35 USC § 103

The rejection of claims 14, 19-20, 23-34 and 38-42 and 44 under 35 U.S.C. 103(a) as being unpatentable over Woolf (cited on PTO Form 892 filed 08/23/05), Olejnik et al. (cited on PTO Form 892 filed 08/23/05), Grigoriev et al. (cited on PTO Form 892 filed 08/23/05) and Yoo et al. (cited on PTO Form 892 filed 08/23/05) is maintained for the reasons of record in the Office action mailed 01/03/2007. The rejection of claim 39 is withdrawn in response to applicant's arguments regarding dendrimer 4. Thus, response to applicant's arguments with regard to the obviousness of using a generation 4 dendrimer as taught by Yoo et al. is obviated.

Applicant's arguments in the response filed 05/03/2007 as to claims 14, 19-20, 23-34, 38 and 40-42 are acknowledged but are not found persuasive. Applicant argues

the results of Yoo et al. demonstrates that lower generation dendrimers, such as a generation 5 dendrimer, only produce moderate activity for delivery of antisense oligonucleotides. Applicant's points to Figure 2, page 1801 of Yoo et al. to make the statement that the levels recognized by Yoo et al. as moderate activity can be "interpretable as little to no activity". Applicant's interpretation of the experiments is clearly not what is taught by Yoo et al. Further, one of skill in the art would not interpret from the results shown in Figure 2 or elsewhere in the reference that an antisense mixed with a generation 5 dendrimer produced "little or no activity". Yoo et al. clearly states in the discussion of Figure 2 in the first full paragraph on page 1801, that while the dendrimer nucleic acid mixture wherein the dendrimer was used in a lower concentration showed only moderate activity, when the concentration of the dendrimer was increased, increased delivery of the antisense molecule was observed and in fact, in the presence of serum, the dendrimer- nucleic acid mixture was more effective when compared to a Lipofectamine. Therefore, from the results taught by Yoo et al., it would have been obvious to use a generation 5 dendrimer as a delivery vehicle to deliver nucleic acids to cells.

Applicant goes on to state that Yoo et al. summarizes, in the first paragraph of the Introduction, that most of the agents are poor in delivering oligonucleotides to cells and therefore concludes that these agents are not likely to be effective *in vivo*. Applicant appears to imply that the "agents" stated by Yoo et al. are dendrimers. This statement is taken completely out of context. A thorough and complete reading of the statement in the context of the entire Introduction section would yield that the "agents"

Yoo et al. refers to are cationic lipids, polypeptides, etc and it is these agents that are unlikely to be effective for *in vivo*. Yoo et al. states the ideal delivery agent should be able to stably bind oligonucleotides, be small in size and promote penetration into cells. It is precisely these characteristics that Yoo et al. demonstrates dendrimers possess and concludes that these dendrimers may be well suited for *in vivo* therapeutic applications. Therefore, given that Yoo et al. outlines the ideal characteristics for a delivery vehicle comprising a nucleic acid and demonstrates dendrimers are effective at delivery nucleic acids to cells and further states that dendrimers are useful for therapeutic applications, it would have been obvious to use a dendrimer, particularly a generation 5 dendrimer as instantly claimed, as a delivery vehicle for nucleic acids.

Applicant states that in assessing the activity of the complexes taught by Yoo et al., numerous factors including dendrimer generation, oligonucleotide concentration, charge ratio and presence of serum are factors which require optimization and "such a large amount of possibilities is beyond routine experiment//tion and optimization". MPEP 2144.05 states: "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Therefore, because Yoo et al. demonstrate the general conditions necessary for assessing the activity of dendrimer – nucleic acid mixture and further demonstrate the routine nature of testing various ratios of dendrimer to oligonucleotide, from 15 ug/ml to 90 ug/ml (see Figure 1 and Figure 2) for optimization of the most efficient ratio for

delivery and gene inhibition, these conditions would not be considered beyond the level of routine optimization.

Applicant submits that while the teachings of Yoo et al. instructs the skilled artisan that a generation 5 dendrimer may have potential applications as a delivery agent, the limited demonstration of highly efficient activity and efficacy combined the numerous parameters necessary for optimization, the teaching of Yoo et al. amount to no more than a mere suggestion for further experimentation. As explained above, because Yoo et al. teach delivery of a nucleic acid using a dendrimer and further demonstrates the general conditions necessary for assessing the activity of dendrimer-nucleic acid mixture and further outlines the routine nature of testing various ratios of dendrimer to oligonucleotide, from 15 ug/ml to 90 ug/ml (see Figure 1 and Figure 2) for optimization of the most efficient ratio for delivery and gene inhibition, these conditions would not be considered beyond the level of routine optimization and would not amount to a mere suggestion for further experimentation.

Applicants argue that Olejnik et al. nor Grigoriev et al. provide any teaching or suggestion regarding using a dendrimer to deliver a nucleic acid and therefore neither alone or in combination with Woolf et al. and Yoo et al. provide a suggestion to produce a delivery mixture comprising a dendrimer and a nucleic acid. Olejnik et al. and Grigoriev et al. were relied upon to teach obvious modifications to nucleic acids and as stated in the previous Office action, one of skill in the art would have been motivated to incorporate a photocleavable biotin because Olejnik et al. teach incorporation of a photocleavable biotin into a oligonucleotide provides a simple

method for purification of oligonucleotides and one of skill in the art would have been motivated to incorporate psoralens into nucleic acids because Grigoriev et al. teach addition of psoralen derivatives to oligonucleotides increase the antisense target affinity and half-life by crosslinking the antisense oligonucleotide to the target. Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant argues that failure of others is a secondary consideration or indicia of non-obviousness and because Kang et al. (submitted by applicant in the response filed 11/07/2006) fails to show success of delivery of a siRNA complexed with a dendrimer. One of skill in the art would not interpret the results of Kang et al. as a failure of success at delivery of a siRNA complexed with a dendrimer. While it is true that Kang et al. demonstrates, with a single experiment, under limited conditions and targeting a single gene expression a P-glycoprotein, that siRNA complexed with a dendrimer did not achieve the same results when compared with an antisense compound, this cannot be interpreted to mean Kang et al. failed to delivery any siRNA to cells. However and more importantly, it must be pointed out that the instant claims are drawn to a delivery mixture comprising a dendrimer and a nucleic acid capable of eliciting RNAi and as stated in the previous Office action mailed 01/03/2007, one would expect to be able to produce a delivery mixture comprising a dendrimer complexed with a nucleic acid capable of mediating RNAi given they are both comprised of nucleic acids. A siRNA is clearly capable of being complexed with a siRNA as demonstrated by Kang et al. (see page 2101) and acknowledged by Applicant as being taught by Kang et al. (see Response

filed 05/03/2007, page 12). Therefore, there was a reasonable expectation of success at producing a delivery mixture comprising a siRNA and a dendrimer.

Lastly, Applicants argue that evidence of unexpected results can be used to rebut a prima facie case of obviousness and submit that the delivery mixture comprising a generation 2 to 5 dendrimer and a nucleic acid capable of mediating RNAi is superior to those compositions described in Yoo et al. Applicants further state the results obtained in Examples 1 and 2 are "far improved as compared to the experiments described in Yoo et al." and would not be expected in view of the teachings of Yoo et al.

First, it must be stated that it is not clear from the explanation of Examples 1 and 2 or any other experiment in the instant specificaiton, specifically what generation of dendrimer is used. Therefore, there cannot be a direct comparison to the experiments taught by Yoo et al., whom use a generation 5 dendrimer, to be able to make the determination that the claimed invention provides evidence of unexpected results. Further, the standard for rebutting an obvious rejection is "that there are new and unexpected results relative to the prior art". The fact that Examples 1 and 2 show evidence that "are far *improved* as compared to the experiments described in Yoo et al." [emphasis added] is not sufficient evidence of *new* and *unexpected* results. Examples 1 and 2 in the instant specification provide, at best, evidence of routine optimization of the general conditions of complexing a nucleic acid with a dendrimer as taught by Yoo et al. and as discussed above, "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine

experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2144.05

As such, the instant invention does not provide evidence of unexpected results and therefore the instantly claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

The rejection of claims 14, 17-24 and 32-44 under 35 U.S.C. 103(a) as being unpatentable over Yoo et al. (cited on PTO Form 892 filed 08/23/05) in view of Hammond et al. (cited on PTO Form 892 filed 08/23/05), Tuschl et al. (cited on PTO Form 892 filed 08/23/05) and McManus et al. (cited on PTO Form 892 filed 08/23/05) is maintained for the reasons of record in the Office action mailed 01/03/2007.

The rejection of claim 39 is withdrawn in response to applicant's arguments regarding dendrimer 4 taught by Yoo et al. argued above. Thus, response to applicant's arguments that it would not be obvious to use a dendrimer 4 as taught by Yoo et al. is obviated. The response to the previous rejection above would apply to this rejection.

Applicant's arguments in the response filed 05/03/2007 as to claims 14, 17-24 and 32-38 and 40-44 are acknowledged but are not found persuasive.

Applicant argues the deficiencies of antisense, namely questionable specificity and incomplete efficacy also include ineffective and inefficient delivery to cells and it is these last reasons, ineffective and inefficient delivery to cells, that do not support a motivation to substitute a siRNA for an antisense molecule. Applicant reasons that because dendrimers have reported problems of toxicity and localization using antisense

compounds, this would support a lack of expectation of success that substitution of siRNA would in fact work given that both antisense and siRNA are both nucleic acids and would be subjected to similar problems.

Applicant's arguments are not convincing. It is unclear where applicant is drawing the conclusion, either from Yoo et al. or another reference, that all dendrimers have reported problems of toxicity and localization. Applicant is invited to provide evidence that this the general perception of dendrimers as a whole. The motivation to substitute a siRNA for a antisense is because of the deficiencies discussed by applicant i.e. questionable specificity and incomplete efficacy. Further, a review of Yoo et al. does not support Applicant's conclusion. Yoo et al. clearly demonstrates dendrimers are efficient delivery vehicles given their stability and small size and demonstrates a generation 5 dendrimer is capable of delivering a nucleic acid to a cell and states that dendrimers are useful in vivo therapeutics. As such, because Yoo et al. outlines the advantages of dendrimers compared to other known agents in the art used to enhance delivery of nucleic acids and because it is well known at the time the invention was made that siRNA are more efficient at silencing gene expression from a target gene, the skilled artisan would have been motivated to substitute a siRNA or microRNA as taught by Hammond et al, Tuschl et al. or McManus et al. for the antisense compound taught by Yoo et al.

Thus in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

The rejection of record of claims 14, 17-24, 32-34 and 38-42 under 35 U.S.C. 103(a) as being unpatentable over Yoo et al. (PTO Form 892 filed 08/23/05) in view of Hammond et al. (Nature 2001, Vol. 2: 110-119), Tuschl et al. (WO 02/44321) and McManus et al. (Nature Review: Genetics 2002) is maintained for the reasons of record in the action in the Office action mailed 01/03/2007.

For clarification, this rejection was originally made in the final Office action mailed 08/07/2007 and maintained in the Office action mailed 01/03/2007. A new rejection using all of the above references was made and included amended claims 35-37 that were not examined in the Office action mailed 01/03/2007 due to improper multiple dependency. Applicant's arguments regarding the above cited references and the response to those arguments would apply to the reasons for maintaining this rejection.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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